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METFORMIN THERAPY FOR PREDIABETES

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Abstract:

Background: *most individuals with glucose intolerance will eventually develop other metabolic abnormalities making them fit the criteria for a diagnosis of diabetes mellitus type 2. This is serious because it means that due to the large number of individuals in those categories, a huge number of diabetes mellitus type 2 cases will be diagnosed soon in the future. Therefore, it has become essential to target individuals in these two categories to detect the defects early and prevent the progression to diabetes mellitus type 2 or delay it for the longest possible period.*

Methodology: *We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: glucose intolerance, prediabetes, diabetes mellitus, health risks associated with pre-diabetes, management of pre-diabetes, metformin*

Aim: *In this review, we aim to study the pathophysiology of prediabetes, the risks associated with it, and the its management with metformin*

Conclusion: *Debates are still present on the best time to start metformin therapy, especially in prediabetic individuals who have a significantly higher risk of developing diabetes mellitus type 2 than the general population. Most studies have shown that proper control of prediabetic individuals is associated with improved outcomes and decreased rates of diabetic conversion. Interventions include lifestyle modifications and metformin therapy. Most studies have found that long-term use of metformin in prediabetic patients can significantly decrease the risk of conversion into diabetes mellitus type 2, and prevent diabetes in some cases.*

Keywords: *Metformin, Pre-Diabetes, Glucose Intolerance*

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INTRODUCTION:

The term 'diabetes mellitus' covers a wide range of metabolic disorders that all show abnormal elevations of blood glucose levels as a result of defective secretion and/or activity of insulin, which is the major hormone in glucose regulation. The thresholds of glucose level to define the presence of diabetes have varied. Generally, they are set according to observations from previous studies of the relation between different blood glucose levels and the presence of diabetic micro and macrovascular events (like retinopathy, neuropathy, and nephropathy) [1].

The term 'glucose intolerance' was first used in the year 1979 by the National Diabetes Data Group and has been used to describe a state of metabolism where the individual does not have normal homeostasis of glucose, but also does not qualify to be diagnosed with diabetes [2]. As the definition state, these individuals can have blood glucose levels that are higher than normal, but they still do not fit the criteria of making a diagnosis of diabetes. Another prediabetic status was first defined in the year 1997 and is having impaired fasting glucose. Both impaired fasting glucose, and glucose intolerance are currently considered prediabetic statuses as they significantly increase the risk of developing diabetes mellitus in the individual. In fact, most individuals who show one of these statuses will eventually develop other metabolic abnormalities making them fit the criteria for a diagnosis of diabetes mellitus type 2. This is serious because it means that due to the large number of individuals in those categories, a huge number of diabetes mellitus type 2 cases will be diagnosed soon in the future. Therefore, it has become essential to target individuals in these two categories to detect the defects early and prevent the progression to diabetes mellitus type 2 or delay it for the longest possible period [3].

Application of lifestyle modifications has been proven in many large trials to achieve desired results in prevention and delay of diabetes occurrence. However, to be effective, they need high compliance. Pharmacological agents, on the other hand, have also shown great promising results, especially metformin that has been largely studied. Clinical trials on metformin were able to prove its efficacy in preventing diabetes mellitus type 2 especially when used by young obese high-risk individuals. Moreover, its safety has been well studied, and was considered safe and tolerable by most individuals.

METHODOLOGY:

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: glucose intolerance, prediabetes, diabetes mellitus, health risks associated with pre-diabetes, management of pre-diabetes, metformin

- **Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was approved by the ethical board of King Abdulaziz University Hospital

Pathophysiology and Diagnosis of Prediabetes

Before the occurrence of diabetes mellitus type 2, dysfunctions in glucose metabolism start to occur and progress for many years. Insulin insensitivity is considered the main dysfunction in diabetic patients and is defined as the blunting of insulin action on the metabolism of glucose. Insulin insensitivity is known to be one of the earliest steps that precede the development of diabetes mellitus type 2. Initially, this insulin insensitivity can be overcome by increased secretion of insulin. However, B-cells of the pancreas will soon show decreased efficacy and ability to compensate and maintain the balance, leading to a progressive state of hyperglycemia [4]. Earliest manifestations of prediabetes and impaired glucose metabolism include [5]:

- impaired glucose tolerance (IGT), where individuals show abnormal postprandial glucose levels with normal fasting glucose.
- impaired fasting glucose (IFG), where individuals show a long-term increase in fasting glucose levels with normal postprandial glucose levels.

In cases of abnormal fasting blood glucose, this can be easily diagnosed with a single blood test. However, to diagnose impaired tolerance, and abnormal postprandial glucose levels, oral glucose tolerance test is used, which is more complicated. A threshold of 110 mg/dL had been used to make a diagnosis of the presence of high fasting glucose, but it was lowered to become 100 mg/dL to detect prediabetes earlier and improve the chances of preventing or delaying the development of diabetes

mellitus type 2 in these individuals. However, the World Health Organization still considers 110 mg/dL the threshold for having abnormal fasting glucose [6].

According to the American Diabetes Association, a diagnosis of prediabetes can be generally made in any individual who show elevation in HbA1c levels that are not high enough to diagnose diabetes mellitus type 2. This is important because it detects individuals at high risk of developing diabetes mellitus type 2 and give the chance to take measures to prevent this [7]. However, in the year 2010, a US study was published and found that elevations of HbA1c levels do not always indicate the presence of prediabetes and can sometimes underestimate or overestimate the presence of glucose metabolism dysfunctions. Therefore, despite being perfect for following patients diagnosed with diabetes mellitus type 2, the use of HbA1c for diagnosis of prediabetes is still debatable and need further studies [8].

When individuals start to develop insulin insensitivity and B-cells destruction, the body will gradually lose its ability to regulate glucose levels. In fact, when a patient develops glucose intolerance, we can know that they have already lost about 50% of the functions of B-cells. When this loss becomes 80% of B-cells, the patient will progress to diabetes mellitus type 2 [9].

HEATLH RISKS ASSOCIATED WITH PREDIABETES:

Progression to diabetes

Rates of conversion from prediabetic status to a diagnosis of diabetes mellitus type 2 vary among populations and change according to the exact definition of prediabetes. A previously published meta-analysis has studied the evolution of prediabetes to diabetes, and concluded that individuals with glucose intolerance have a 6% annual risk of progressing into diabetes mellitus type 2, while individuals with impaired fasting glucose have a 9% annual risk of progressing into diabetes mellitus type 2. On the other hand, individuals who have both glucose intolerance and impaired fasting glucose have significantly higher annual risk that can be as high as 19% of developing diabetes mellitus type 2 [10]. However, a big limitation for this meta-analysis was it only included studies that were published prior to 2004. Further studies were conducted and included newer data and reached nearly similar conclusions. Interestingly, one of these large studies, that was conducted by the Diabetes Prevention Program, found that the control group had a 11% annual risk of developing diabetes [11].

A large US study on several ethnic groups also confirmed that the annual risk of developing diabetes mellitus type 2 in patients with impaired fasting glucose was higher than 4% [12]. Another study conducted in the Toranomon Hospital found that annual incidence of diabetes mellitus type 2 was 7% and 9%, in individuals with Hb1Ac between 5.7%-6.4%, and individuals with impaired fasting glucose, respectively [13]. A similar study was conducted on Chinese population and found that the overall incidence of diabetes mellitus over the study period (which continued for twenty years) was more than 90% in patients who had impaired fasting glucose at entering the study [14].

Experts and researchers in this field have suggested that the use of continuous risk scores will be more accurate in predicting diabetes risk than the use of dichotomous scores. Additionally, rather than only using the presence of impaired fasting glucose or glucose intolerance to predict the risk, more accurate models add other demographic and health-related factors to accurately predict this risk. These factors include individual's age, gender, race, fasting blood glucose, blood pressure, HDL levels, body mass index, and family history of diabetes or metabolic syndrome [15].

Nephropathy and kidney disease

The presence of a correlation between having kidney disease, and the development of prediabetes, which will later progress to diabetes, has been studied and proven by many previous studies. However, this correlation still does not prove the presence of any causality, and it may be simply due to the presence of other confounding factors that predispose to the development of both nephropathy and prediabetes [16].

Neuropathies

Patients who suffer from variability of heart rate or other cardiac autonomic dysfunctions have been found to have higher incidence of prediabetes [17]. Other neurological dysfunctions associated with prediabetes include reduced cardiac modulation of parasympathetic activity and erectile dysfunction. Assessment of neuropathies with non-invasive techniques has found that individuals with glucose intolerance suffer from abnormalities in cardiovascular reflexes, higher hyperesthesia rates, higher hypoesthesia rates, and/or elevated threshold for detecting heat [18]. In addition, evidence suggests that these individuals can develop polyneuropathy,

small fiber neuropathy, and painful neuropathy more often than the general population [18]. These results raise concerns on the involvement of autonomic, pain and temperature nerve fibers in the pathogenesis of prediabetes and the development of diabetes mellitus type 2.

Retinopathy

In a previous large study, up to 8% of prediabetic individuals showed signs of retinopathy [19]. Several later studies confirmed the presence of a correlation between neuropathy and prediabetes. However, results varied between these studies based on different populations and methods for detecting and diagnosing retinopathy [20].

Macrovascular disease

Many studies have suggested the presence of a correlation between macrovascular pathologies and prediabetes. However, it is still not clear whether prediabetes itself causes these pathologies, or they are a result of the underlying progression to diabetes mellitus type 2. In addition, observational studies have confirmed the presence of high prevalence of anginal disease in prediabetics, but these results are liable to confounding factors and need better assessment in larger, better-controlled studies [21].

Principles of Management of Prediabetes

Any individual who has a high risk of developing diabetes mellitus type 2 must be screened for the presence of prediabetic status and underlying cardiovascular disease. These individuals include obese individuals, and females who previously had gestational diabetes. The best most initial step in correcting prediabetes remain to be lifestyle modifications which mostly rely on better diet and regular exercise to lose weight, especially in obese individuals. In addition, many studies have suggested that pharmacological interventions can be effective in prediabetic patients for the prevention or delay of diabetes development. These interventions include drugs that are usually used in diabetes mellitus type 2 (metformin and other oral hypoglycemics), and interventions that aid in weight loss (like bariatric surgery) [22].

Apart from lifestyle modifications, the only pharmacological agent that showed significant results in preventing diabetes mellitus development when used in prediabetic patients is metformin. This success has been proven in several trials, that also showed its relative safety and tolerability in these individuals along with its availability and low costs. Currently, most countries do not indicate metformin prescriptions in prediabetic patients. However, this is expected to change in the near future due to its proven efficacy [22].

Pharmacologic Properties of Metformin

Principal Therapeutic Sites of Action of Metformin

The mechanism of action of metformin is by the enhancement of insulin actions in hepatocytes, which will lead to the reduction of glucose production in the liver. These improvements in insulin actions that result from metformin use, apply also to the skeletal muscles and lead to improved disposal of non-oxidative glucose. All these actions work together to decrease levels of glucose in the blood in individuals with high blood glucose. Additionally, metformin has a minimal risk of developing hypoglycemia with its use [22].

Another mechanism of metformin action is its ability to increase anaerobic metabolism in the wall of intestines, which will play a significant role in decreasing blood glucose [23]. Additionally, metformin can lead to elevation of GLP-1 levels by increasing its secretion and inhibiting its destruction. Metformin can also upregulate GLP-1 receptors expression on B-cells of the pancreas [24].

Molecular Mechanisms for the Antihyperglycaemic Actions of Metformin

Metformin has been shown to mechanically inhibit the respiration of mitochondria at the level one of the respiratory chain. This will lead to a significant shift in the balance of cellular energy leading to higher AMP kinase activity, which will further enhance insulin actions and decrease gluconeogenesis in the liver [25].

Some studies have also suggested that the use of metformin can improve DPP4 inhibitors actions by increasing DPP4 activity and GLP-1 secretion. To achieve its actions properly, metformin depends on cellular transportation through the OCT1 transported. Therefore, polymorphisms of this molecule have been shown to alter metformin efficacy in diabetic patients. These mechanisms have been proven to be beneficial in improving prediabetic status and decrease the progression into diabetes mellitus. However, the involvement of metformin in prediabetes improvement is still not clearly understood and need further research [26].

Safety and Tolerability

Adverse events of metformin are mainly related to

the digestive system and include mainly diarrhea, which can be decreased when the drug is started with low doses and increased gradually. Preparations of metformin that have longer duration of action are available and have been associated with improved tolerability and decreased risk of diarrhea. Apart from diarrhea, the use of metformin has also been associated with the development of lactic acidosis. However, rates of developing lactic acidosis when the drug is used right are extremely low [27].

Contraindications to the use of metformin include the presence of severe cardiac morbidities, and kidney disease, as these patients have relatively higher risk of developing lactic acidosis when they are on metformin therapy. Generally, prediabetic individuals have significantly lower risk of developing lactic acidosis following metformin treatment when compared to diabetic patients.

Some studies have suggested that metformin therapy can be associated with the development of vitamin B12 deficiency and its associated neuropathy, which can sometimes be clinically similar to diabetic neuropathy. In a study that continued for more than four years, the risk of developing vitamin B12 deficiency was 7% higher in patients with metformin therapy when compared to patients on placebo [28]. Another meta-analysis that included 29 trials with overall 8,089 patients showed that vitamin B12 deficiency was significantly higher with metformin therapy versus other groups. Therefore, patients on metformin therapy should always have their vitamin B 12 levels monitored and receive vitamin supplementations when these levels decrease below normal levels [29].

Principal Diabetes Prevention Trials with Metformin

Prediabetics have been shown to have significantly reduced risk of developing diabetes mellitus type 2 when they were treated with metformin. These results were proved on different populations including the US, Indians, Chinese, Canadians, and Pakistanis [30-34].

Lifestyle modifications have been found to also be effective n decreasing the risk of diabetes development, and therefore should be recommended all prediabetics, especially who have cardiovascular risks, and despite metformin therapy or any other therapies. Other interventions that have been found beneficial in the management of prediabetes and prevention of diabetes include the use of α-glucosidase inhibitors, thiazolidinediones, and bariatric surgery. An analysis of data from the STOP-NIDDM trial has concluded that decreased rates of both cardiac diseases and hypertension in prediabetic patients who used acarbose when compared to prediabetic patients who were on placebo [35].

The Diabetes Prevention Program (DPP)

This program included more than three thousand prediabetic individuals who were randomized to different lifestyle modifications, metformin, and placebo. These patients were studied for the development of diabetes. After about three years, this study finished and concluded that intensive lifestyle modifications were better than metformin in prevention of diabetes in prediabetic individuals. Having lower fasting glucose levels, less weight, and younger age were all associated with less rates of developing diabetes [36].

Further Analysis from the DPP

Levels of adherence to metformin therapy and lifestyle modifications in the DPP study were found to be lower in younger patients [37]. The presence of a prior history of gestational diabetes in prediabetic females was associated with significantly higher rates of developing diabetes mellitus type 2 following prediabetes. In these females, both metformin and lifestyle modifications led to similar effects on decreasing risk of developing diabetes mellitus type 2 [38].

Patients who applied intensive lifestyle modifications showed significant elevation in adiponectin blood levels, which was not observed in patients on metformin or placebo. This elevation in adiponectin blood levels is believed to play an important lore in lowering the risk of diabetes in prediabetic individuals [39]. Alcoholism and alcohol abuse were also associated with decreased insulin levels and activity [40].

CONCLUSION:

When managing patients with diabetes mellitus type 2, metformin remains to be the mainstay of treatment to improve glycemic control and glucose regulation. However, debates are still present on the best time to start metformin therapy, especially in prediabetic individuals who have a significantly higher risk of developing diabetes mellitus type 2 than the general population. Most studies have shown that proper control of prediabetic individuals is associated with improved outcomes and decreased rates of diabetic conversion. Interventions include lifestyle modifications and metformin therapy. Most studies

have found that long-term use of metformin in prediabetic patients can significantly decrease the risk of conversion into diabetes mellitus type 2, and prevent diabetes in some cases. This effect of metformin varies among populations and seems to be affected by different factors in individuals. Therefore, further studies are still needed to study metformin exact effects on different subpopulations of prediabetic individuals.

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